# *Is there a neuropathology difference between mild cognitive impairment and dementia?*

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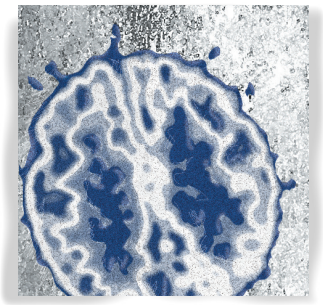

Mild cognitive impairment (MCI) represents a clinical construct that identifies an intermediate state of cognitive function between that of healthy aging and memory and cognitive deficits associated with frank dementia. In most cases, the definition of MCI is intended to be applicable to those persons in the intermediate state of memory and cognitive impairment who are destined, if they live long enough, to meet criteria, at least clinically, for dementia or Alzheimer's disease (AD). Although the causes of dementia and therefore MCI can vary widely, we will limit the discussion of the neuropathology of MCI to the role of postmortem neuropathological and neurobiological features that are commonly associated with AD. The criteria and definitions for MCI as initially described by the Canadian Study of Health and Aging,[1,2] Reisberg et al,[3-7] and Flicker[8] in the late 1980s were relatively broad and permissive.

*The number of studies that have investigated the neuropathology of mild cognitive impairment (MCI) is small, but growing. In this paper we have restricted our focus to the consideration of the presence and extent of postmortem findings relevant to the neuropathology of Alzheimer's disease. We have drawn from studies that have investigated the postmortem neurobiology of the brains of persons with cognitive function at the interface between unimpaired normal function and mild but definite dementia. The data derived from these studies suggest that i) the brains of persons with MCI evidence significant neuropathological and neurobiological changes relative to those without cognitive impairment; ii) in general, the neuropathological and neurobiological changes are qualitatively similar to those observed in the brains of persons with frank AD-like dementia; and iii) the neuropathological and neurobiological brain changes associated with MCI are quantitatively less than those of persons who meet criteria for dementia. Thus, the available, albeit limited, data suggests that MCI is associated with the early stages of the neurobiological and neuropathological changes that culminate in the florid lesions of AD; including the accumulation of neuritic plaques, neurofibrillary tangles, synaptic and neurotransmitter associated deficits, and significant neuronal cell death.*



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## Selected abbreviations and acronyms

| | |
|---|---|
| ***AD*** | *Alzheimer's disease* |
| ***CDR*** | *Clinical dementia rating* |
| ***MCI*** | *mild cognitive impairment* |
| ***MRI*** | *magnetic resonance imaging* |
| ***NBM*** | *nucleus basalis of Meynert* |
| ***NFT*** | *neurofibrillary tangles* |
| ***NP*** | *neuritic plaques* |

Subsequent clinical studies suggested that some individuals with MCI remain in this intermediate stage of cognitive function for longer periods of time than expected. The criteria/definitions were then further refined to include amnestic MCI (ie, predominantly memory impairment cases expected to be predisposed to progress to dementia) and nonamnestic MCI (ie, non-memory-associated mild cognitive impairment cases who may not necessarily progress to frank dementia).[9,10] Amnestic and nonamnestic MCI can be further subdivided to include single or multiple cognitive domains (see refs 11,12 for an MCI algorithm). As in the diagnosis of AD and dementia, the criteria for cognitive impairment in any domain are applicable to a change in cognition, memory or otherwise, from a prior level of functioning. Other classification schemes have also been used to define the cognitive space between healthy cognition and dementia.[9,13] One example is the use of the clinical dementia rating (CDR)[14] scale and definition of MCI as questionable dementia (CDR score of 0.5). Notably, as indicated below, many studies of the neuropathological features of MCI have used the CDR=0.5 metric to define MCI. It must be emphasized, however, that despite the fact that MCI is often used as a global framework to define the space between no cognitive impairment and frank dementia, different conceptualizations and definitions vary considerably and influence how individuals are classified. One recent study[15] that explored the usage of four commonly used definitions and criteria found considerable variation between them (from 5.9% to 32.4% of studied individuals classified as MCI depending on the metric used). Of the 34 people studied, no subject was classified as MCI by all four definitions.

The neuroimaging literature of pathological changes associated with MCI is more extensive than the postmortem literature. This is in part to due to the progression of persons with MCI to more severe forms of dementia before they die and come to autopsy. The neuroimaging literature[16-23] implicates pathological changes, such as atrophy and sclerosis, in the hippocampus and entorhinal cortex, and the likely development of amyloid plaques based on molecular neuroimaging, by positron emission tomography (PET) using an amyloid-β-peptide (Aβ) ligand known as Pittsburgh Compound B (PiB).[24,25] The validity of PET studies with PiB has been bolstered by a limited number of in vivo imaging and postmortem neuropathology studies,[26,27] and one recent study that combined PiB-PET with neuropathological study of brain biopsy specimens.[28,29] The neuroimaging literature in MCI has been reviewed recently.[11,30]

An issue that influences how we interpret postmortem neurobiological studies of MCI and dementia is the way that neuropathological criteria are applied and the way that experiments are designed. It is important to recognize that neuropathological criteria such as the CERAD[31] or NIA/Reagan[32] criteria are probabilistic constructs designed to distinguish between persons with significant AD neuropathology and those without. The probabilistic nature of these criteria stems from the recognition that there are significant instances of persons with no cognitive impairment who nevertheless evidence unusually high levels of AD-associated neuropathology,[33,34] and instances of persons with clinically diagnosed AD-like dementia who present with little or no discernable neuropathology. In addition, age, the most significant risk factor for dementia, also plays a role in the extent of AD-associated neuropathology observed in the brain, irrespective of the presence or absence of dementia symptoms. Thus, if questions regarding the presence, absence, or extent of neuropathologic lesions or neurobiological changes are framed in the context of whether persons with MCI meet neuropathological criteria for AD, the results may lead to very different conclusions than if the questions are framed within the context of whether persons with MCI present with lesion densities or neurobiological changes that are different from those without cognitive impairments. In general, the brains of persons with MCI do not meet neuropathological criteria for AD, but they nevertheless evidence pathological features that are qualitatively, but not quantitatively, AD-like (please see below). An illustrative example is a study of the association of neuritic plaques with cognitive compromise as defined by the CDR.[35] Persons with no cognitive impairment were compared with those with different levels of impairment. Persons with CDRs of 0.5 (ie, MCI), had cortical neuritic plaque densities that were significantly higher than that of persons with intact cognition. Yet, the

majority of the studied sample with CDR scores of 0.5 and even those with CDR scores of 1 did not meet accepted neuropathological criteria for AD.[31,32,36] Similar results have been reported using different MCI classification schemes and different metrics of AD-associated lesion densities (eg, ref 37).

## General neuropathology

The majority of the studies of the neuropathology of MCI, especially degenerative/amnestic MCI,[11,12] suggest that in most instances MCI is associated with a less fervent manifestation of the neuropathologies that are generally associated with dementia. Unselected MCI samples derived from memory clinic or general geriatric populations evidence a variety of neuropathologic lesions such as those associated with diffuse Lewy body disease, cerebrovascular disease, ischemic changes and hippocampal sclerosis, argtrophilic grain disease, Parkinson's disease, and, of course, AD (eg, refs 37-40). Nearly invariably, the extent of these lesions is considerably less than those observed in persons with frank dementia. In general, relative to persons with intact cognition, the frequency of AD-associated neuropathology in persons with MCI, especially those with amnestic MCI, is significantly greater than other neuropathologic lesions associated with dementia.[40,41]

## Hallmark lesions of AD

Alzheimer's disease is characterized by extracellular neuritic plaques (NP) and intracellular neurofibrillary tangles (NFT).[35,41-47] As mentioned previously, the extent, distribution, and density of these lesions are used by most diagnostic and staging strategies for AD. Most studies of MCI have shown that the density and distribution of these hallmark lesions and their less "mature" lesion variants (eg, NP—diffuse plaques, cored plaques; NFT—pre-NFT hyperphosphorylated or conformationally altered tau) is significantly increased in the brains of persons with MCI.[35,38,39,42,44,48-50] Early studies by Morris et al[48,49] showed that persons with CDR scores of 0.5, ie, questionable dementia/MCI, evidenced statistically significant increases in the density of plaques, especially diffuse plaques, in the temporal cortex. The density of plaques increased with increasing dementia severity and the proportion of plaques shifted from diffuse to more mature variants (eg, cored and neuritic). Our studies of neuritic plaques[35] showed a similar pattern where persons with CDR=0.5 evidenced significantly greater number of NPs in the neocortex than age-matched cognitively intact controls, but fewer NPs than persons with frank dementia (ie, CDR>1). Similar changes were noted recently in a study where the definition of MCI was restricted to those persons with amnestic MCI as defined by Petersen et al.[10,11,51] In that study,[39] the numbers of neocortical diffuse plaques were not significantly elevated in MCI, but the numbers of NPs were significantly higher than those in persons with intact cognition. Since the pathogenic constituent of NPs is the Aβ peptide, it is not surprising that Aβ levels in the brains of persons with MCI are also significantly elevated.[52-54] Just as diffuse plaques may represent premature NPs, oligomeric forms of Aβ may precede the diffuse aggregates and represent an even earlier neurotoxic form of Aβ.[55] The question of the association of oligomeric forms of Aβ in MCI is an area of active current investigation by many laboratories (see below). As mentioned previously, these observations of plaque involvement in MCI are consistent with neuroimaging/PET studies of MCI using PiB.[28,29]

Generally similar conclusions can be drawn regarding the involvement of NFTs in MCI.[33,47,50,56-60] However, the precise distribution of NFTs within neocortical and medial temporal lobe structures and the phosphorylation or conformational state of the tau protein constituent of NFTs may be critical factors. Several studies have found that the density of NFTs in the hippocampus and the parahippocampal gyrus as well as the amygdala increase significantly in persons with MCI (eg, refs 39,49). Most studies find that the NFT involvement in neocortical regions is associated with more advanced cognitive impairment, supporting the staged development of NFT pathology as a function of AD progression.[61,62] The development of early NFT pathology and its progression is further supported by cellular studies. Stereological analyses have shown that, at least in the neocortex, MCI or early AD-associated NFTs develop first in degeneration-susceptible large neurons of layers III and V of the frontal cortex, implicating long-track association circuits of the brain.[47] Multivariate analyses of NFTs with an emphasis on early conformational changes of tau in the frontal cortex support these observations.[42] On the other hand, other studies (eg, refs 44,63) have noted an age-dependent increase in NFTs, like those cited above, but they have found NFT association with cognitive function relatively late in the course of disease. A possible explanation of these apparently discrepant results may lie in the

way that NFTs develop. Just as NPs are thought to evolve (from diffuse to cored to neuritic), NFTs develop gradually through changes in protein structure. NFTs are comprised of paired-helical filaments that are aggregates of the microtubule-associated protein tau[64-68] that have undergone abnormal conformation and phosphorylation.[69-72] Several studies suggest that even when an association between MCI and histopathological indices of NFTs is not identified, changes in the phosphorylation or conformation state of tau are associated with MCI (eg refs 42,73). In addition, recent studies suggest that the neurofilament protein tau within the AD-vulnerable cholinergic neurons of the nucleus basalis of Meynert (NBM)[74] and noradrenergic neurons within the brainstem locus ceruleus[75] become conformationally altered or hyperphosphorylated in MCI.[60]

## Neuronal and synaptic loss

Although NPs and NFTs are hallmark and diagnostic lesions for AD, their net effect on cognitive function may be expressed through cell death and/or loss of synapses. Only a few studies have examined neuronal or synaptic loss in MCI directly, eg, refs 76-80. Several of these studies[76,78,81] used stereological techniques and found significant loss of neurons in the frontal cortex, the entorhinal cortex and the CA1 field of the hippocampus. An interesting feature of one of these studies[76] was that the neuronal loss exceeded the number of NFT-bearing neurons. This observation could suggest that in addition to NFTs, other factors influence neuronal loss in MCI and AD; but it can also be argued that the greater neuronal loss reflects the death and elimination of NFT-bearing neurons, and the survival of other NFT-bearing neurons that have not yet been eliminated from the neuronal pool. On the other hand, other studies[79] have noted that detectable cell loss does not occur in the brains of persons with MCI, but is evident in the brain of more cognitively impaired early AD persons. Credence for this hypothesis can be derived by the observation that in at least one of the studies reporting MCI-associated cell loss,[78] the subjects included in the MCI group evidenced sufficient NP and NFT lesions to meet diagnostic criteria for AD. This observation raises the possibility that persons classified as MCI in this study were in a more advanced stage of cognitive impairment than those assessed in some of the other studies (eg, ref 79). Clearly, the number of studies that have investigated the question of neuronal loss in MCI, and the number of cases of MCI samples in each of these studies is too small to justify firm conclusions. However, the cited studies all suggest that neuronal loss is a feature of cognitive compromise that can be observed early in the dementing process, even if absent at the very earliest stages of impairment.

That more subtle cellular changes occur also in MCI is supported by recent studies that suggest that, while some neurons are lost in MCI, others, especially those in the cerebral cortex, hippocampus, and NBM, undergo hypertrophy of their nuclear volumes.[82,83] It has been hypothesized[83] that these cellular changes may reflect a compensatory state that forestalls cell death in MCI. Although the numbers of studies are still very limited, there is growing emphasis on exposing the neurobiological mechanisms responsible for cell death in MCI. The toxicity of Aβ and Aβ oligomers mentioned above is one example, as is the susceptibility of some neurons to oxidative stress[84,85] and the expression and response to neurotrophic factors.[86-88] One recently emergent concept that is consistent with neuronal loss in MCI and AD is the abnormal re-execution of cell division/cycle programs in neurons and the abnormal expression of cell-cycle related genes and proteins.[89-91] Unquestionably, these divergent mechanisms may not be mutually exclusive and many other cellular processes are likely to play important roles in MCI-associated cell loss. These and other similar studies underscore the clear imperative for future research to more fully describe the mechanistic processes that contribute to neuronal death.

Early studies (eg, ref 74), that have since been replicated multiple times, showed that the cholinergic neurons of the NBM were especially vulnerable to degeneration in AD. This finding was highly consistent with even earlier observations that the activities of cholinergic enzymes are significantly reduced in AD.[92-94] Several studies (eg, refs 95,96) indicated that although the cholinergic deficits in AD were profound, they became manifest only in the late stages of cognitive impairment. More recent reports[97,98] have suggested that MCI is associated with more subtle cholinergic abnormalities that may be indicative of compensatory changes. These detailed studies of MCI found that the activities of cholinergic marker enzymes rose in multiple cortical regions and in the hippocampus of persons with MCI, but then returned to levels comparable to that of nondemented individuals in early AD and early dementia cases before decreasing to below normal in advanced AD. That the MCI-associated

changes in the activities of cholinergic marker enzymes are likely related to changes in NBM neurons has been shown by elegant gene expression profiling studies of individually dissected neurons.[87] This study showed that the composition of neurotrophin/cholinotrophic response elements in individual cholinergic neurons of the nucleus basalis of Meynert is significantly altered in MCI.

A parsimonious corollary to neuronal loss is that it should lead to a decrease in the number of synapses. However, proliferation of synapses compensatory to neuronal loss could also occur, as could reductions in synaptic numbers, proteins and function in the absence of neuronal loss. Early pioneering studies, (eg, refs 99-101), suggested that synapse loss was a strong correlate of cognitive compromise in AD, but these studies did not address the question of synapse loss in MCI directly. Unbiased stereological studies[77,102] have shown that there is indeed significant synaptic loss associated with MCI in the dentate gyrus and the CA1 field of the hippocampus[77,102] and that the magnitude of synaptic loss increases with increasing cognitive impairmant.[77] Many neurobiological mechanisms can be involved in this MCI-associated loss of synapses, including toxicity of Aβ oligomers.[103] More biochemical studies[104] have suggested that the changes in synaptic function may occur non-uniformly in different parts of the brain and that different synapse-associated proteins, including markers of dendritic spine plasticity (drebrin), may be differentially affected in MCI.

## Neuropathology of MCI in the oldest old

Until recently, most studies of the neurobiological substrates of dementia and AD have focused on persons in the 65 to 85 years of age range or have not specifically differentiated between different age groups within the elderly population. However, US Census Bureau data and projections[105,106] show that the number of Americans over the age of 85 (4.4 million in 2001) will rise significantly by 2010 to 5.8 million and will quadruple to 19.3 million by 2050 (http://www.census.gov/population/www/projections/natdet-D1A.html). Of these 19.3 million, 8 million are predicted to develop dementia,[107] with the prevalence of dementia increasing from 13% in 77- to-84 year-olds to 48% in persons 95 years old and older.[108] Similarly, the incidence of dementia increases from 1% at age 65 to 21% to 47% at ages 85 and older.[109-111] Only recently have studies begun to distinguish between "young-old," often defined as those younger than 85 or 90, and oldest-old individuals (persons over the age of 85 or 90). That understanding the neurobiological substrates of dementia and MCI in this age group is important is highlighted by a recent study[112] suggesting that even after controlling for physical disorders, 5-year mortality in persons 95 years and older is significantly higher in demented individuals than in those who are cognitively intact (96% vs 73%, respectively). In fact, dementia was a stronger predictor of mortality in this population than cardiovascular disease, cancer or male sex. The importance of this distinction has become even more apparent from recent evidence suggesting that the neuropathological substrates of dementia may be different in these two broad age categories. Accumulating evidence suggests that nonagenarians and centenarians display different patterns of cortical vulnerability to the neurodegenerative process compared with younger elderly, and it is not known whether correlations between clinical severity and neuropathological stages remain valid in this age group. Several investigations have noted that oldest-old participants who die with dementia frequently do not have the high amounts of the hallmark NP and NFT neuropathological lesions generally associated with dementia and/or AD[113-121] (but see ref 43). One of these studies directly compared the density of neocortical and hippocampal NPs and NFTs in the brains of young-old individuals with CDR scores of 0.5, to similarly impaired oldest-old persons.[121] As expected from the foregoing, a relatively high number of NPs and NFTs were associated with CDR 0.5 in young-old individuals, but the density of NPs and NFTs was not significantly higher in the brains of CDR 0.5 oldest-old persons. The failure of NFT-based neuropathological staging to distinguish between persons without cognitive impairment and those with MCI has also been reported in nonagenarians.[122] Interestingly, the association of synaptic abnormalities and dementia appear to be relatively constant between young-old and oldest-old persons with frank dementia[120] raising the possibility that the association of synaptic proteins with MCI noted in young old persons (see above) will also be true of oldest-old persons with MCI. Even when evidence of MCI associated neuropathology is found in the oldest-old, the neuroanatomical distribution of the lesions appears to vary from that of young-old persons. One quantitative study[46] that investigated the distribution of NPs and NFTS within the different fields of the hippocampus in mild AD cases found modest associations

of NFTs in the CA2 field of the hippocampus in the oldest-old, whereas NFTs in the CA1 field, which is more closely associated with dementia in younger persons, appeared to be relatively spared.

## Concluding remarks

Given the clinical relevance of MCI and its importance and implications for the development of treatment approaches for dementia in the elderly, it is disappointing that direct postmortem and neurobiological studies of MCI are insufficient for firm conclusions. Many of the existing studies are marred by small sample sizes, insufficient clinical characterization, and experimental and practical constraints on consideration of crucial variables such as age, symptom duration, and sex. Despite these limitations, the available data suggests that similar to the continuum of cognitive impairment, the AD-associated neurobiology and neuropathology of MCI are typified by prediagnostic mild changes that are qualitatively similar to those associated with the pathophysiology of AD dementia. Neuropathological, anatomical, and neurobiological studies of MCI in the oldest-old are even more sparse than age-indiscriminate studies or studies in young-old persons. ❑

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### *¿Existe una diferencia neuropatológica entre el deterioro cognitivo leve y la demencia?*

*El número de estudios que han investigado la neuropatología del deterioro cognitivo leve (DCL) es pequeño, pero creciente. En este artículo el foco de atención se ha centrado en la presencia y extensión de los hallazgos postmortem relevantes en la neuropatología de la Enfermedad de Alzheimer (EA). Se ha recurrido a estudios que han investigado la neurobiología postmortem de cerebros de personas con función cognitiva en la interfaz entre la función normal sin deterioro y la demencia confirmada, pero leve. Los datos derivados de estos estudios sugieren que: 1) los cerebros de personas con DCL evidencian cambios neuropatológicos y neurobiológicos significativos en relación con los sujetos sin deterioro cognitivo, 2) en general, los cambios neuropatológicos y neurobiológicos son cualitativamente similares a los observados en los cerebros de personas con franca demencia tipo EA y 3) los cambios cerebrales neuropatológicos y neurobiológicos asociados con el DCL son cuantitativamente menores que los de personas que cumplen los criterios para demencia. Por lo tanto, la información disponible - aunque limitada- sugiere que el DCL está asociado con las etapas precoces de los cambios neurobiológicos y neuropatológicos que culminan en las lesiones floridas de la EA, incluyendo la acumulación de placas neuríticas, ovillos neurofibrilares, déficit sináptico y de neurotransmisores asociados, y significativa muerte celular neuronal.*

### *Y a-t-il une différence neuropathologique entre le déficit cognitif léger et la démence ?*

*Le nombre d'études ayant analysé la neuropathologie du déficit cognitif léger (DCL) est faible mais croissant. Cet article s'intéresse exclusivement à l'existence et à l'importance des observations* postmortem *applicables à la neuropathologie de la maladie d'Alzheimer (MA). Nos conclusions sont issues d'études ayant analysé la neurobiologie* postmortem *de cerveaux de personnes souffrant d'une fonction cognitive intermédiaire entre une fonction normale non altérée et une démence légère mais constituée. Les données issues de ces études montrent : 1) les cerveaux des personnes ayant un DCL manifestent des changements neuropathologiques et neurobiologiques significatifs en comparaison de ceux indemnes de déficit cognitif ; 2) en général, les changements neuropathologiques et neurobiologiques sont qualitativement identiques à ceux observés dans les cerveaux de personnes ayant une démence franche semblable à la MA ; et 3) les modifications cérébrales neuropathologiques et neurobiologiques associées à la DCL sont quantitativement moins importantes que celles des personnes atteintes de démence. Ainsi, les données disponibles, bien que limitées, suggèrent que le DCL est associé aux stades précoces des changements neuropathologiques et neurobiologiques qui mènent aux lourdes lésions de la MA, comprenant une accumulation de plaques séniles, des dégénérescences neurofibrillaires, des déficits associés aux synapses et aux neurotransmetteurs et une mort cellulaire neuronale significative.*

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